REMARKS

Claims 1-32 were pending in the application. Applicant affirms election of Group I, claims 1-13 and 23-29, with traverse. Claims 14-22 and 30-32 are withdrawn from further consideration without prejudice. Claims 1 and 23 have been amended to add the term "transiently." Support for this amendment can be found throughout the specification, for example, at page 3, line 6. Claim 11 has been cancelled. New claim 33 has been added. No new matter has been added.

Amendment of the claims should in no way be construed as an acquiescence to any of the Examiner's rejections and has been done solely to more particularly point out and distinctly claim the invention, to expedite the prosecution of the application. Applicants reserve the right to pursue the claims as originally filed in this or a separate application(s).

Rejection of Claims 1, 3-13 and 23-29 under 35 U.S.C. 112 first paragraph

Claim 1, 3-13 and 23-29 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the enablement requirement for containing subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention. In particular, the Office Action states that:

> "the chronic expression of angiogenesis modulating agents, such as VEGF, is detrimental to the tissue by causing vascular abnormalities (See specification, Pg. 29). . . . Therefore, one would have to transiently transfect the population of cells with a plasmid that encodes for the angiogenesis modulating agent so that the VEGF, or other angiogenesis modulating agent is expressed transiently. Accordingly, ...one would have to chose transfected cells that would only transiently express the angiogenesis modulating agent, therefore stably transfected cells would not be suitable for use in the method. Thus, the requirement of claim 10, wherein the step of transfecting cells comprises selecting stably transfected cells, does not enable the method of augmenting organ function."

Although applicant disagrees with the basis of the rejection, applicant has amended independent claims 1 and 23, and dependent claims thereof, to add the term "transiently" transfected. As amended, these claims are drawn to a method for organ augmentation that requires *transiently* transfecting a population of cells with a plasmid encoding an angiogenesis

modulating agent. These *transiently* transfected cells are then implanted into a target tissue region where the cells will express the angiogenesis modulating agent, which induce assimilation and differentiation of cells in the target region.

Applicant clearly teaches how to transfect cells in a *transient* manner such that the transfected cells, once delivered to the target site, are able to express the angiogenesis modulating agent (e.g., VEGF) for a limited time period of time to increase the angiogenesis modulating agent at a localized region. After such period of time, the cellular production of VEGF is diminished due to the transient nature of the transfection. As a result, the amount of VEGF decreases over time without reaching toxic levels. Thus, the amount and time of VEGF release is controlled to induce assimilation and differentiation of cells in the target region to allow augmentation of organ function, but not to cause an adverse toxic effect. Accordingly, the Examiner is respectfully requested to withdraw the rejection.

Claim 11 has been cancelled, thereby rendering the rejection moot with regard to this claim.

Rejection of Claims 5-7 and 23-29 under 35 U.S.C. 112 Second Paragraph

Claim 5-7 and 23-29 are rejected under 35 U.S.C. 112, second paragraph as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention. In particular, the Office Action states that:

> "claim 5 requires the method of claim 1 to further comprise co-administering a second population of cells. Claim 6 requires the second population of cells to comprise undifferentiated cells. Claim 7 requires the second population of cells to comprise vascular endothelial cells. Claims 23-29 also require one cell population to be transfected with a plasmid encoding for an angiogenesis modulating agent and co-culturing the transfected cell population with a second cell population. However, it is not clear if the second cell population (the non-transfected cell population), in either method, effects the augmentation of the organ function, as it does not appear to have an integral role in the method."

Applicant respectfully traverses the rejection. The invention can use a single population of cells that have been transfected with an angiogenesis modulating agent. The cells of the single population are undifferentiated cells that can be differentiated and assimilated in the target

region after delivery. Alternatively, two populations of cells can be used, where one population of cells are undifferentiated and can assimilate in the target region, while the other population of cells is transfected with the angiogenesis modulating agent, and may or may not be assimilated into the target region (*See* page 30, lines 4-13, of the specification).

Thus, the additional population of cells, does indeed play an integral role in the method of the invention, and affects augmentation of the organ function whether or not it is assimilated.

The Office Action further asserts that:

> Applicant's claim 23 is directed to a method for augmenting organ function comprising: culturing at least one population of cells on a matrix material to produce an organ construct capable of differentiating in vivo to replace or augment organ function; transfecting a second population of cells with a plasmid encoding an angiogenesis modulating agent; and implanting the organ construct and the transfected cells in vivo at a target site. However, it is not clear if it is required that the organ construct and the transfected cells be implanted at the same target site in vivo, or if they have any interaction at all in vivo. Claims 24-28 have the limitation of claim 23, and thus are rejected on the same basis.

Although Applicants disagree with the basis of rejection, Applicants have amended claim 23 to add "a first population of cells" and "one" target site, thereby more clearly defining that the organ construct with the first population of cells, and a second population of cells transfected with the plasmid encoding an angiogenesis modulating agent are both implanted at the same single target site *in vivo*. New claim 33 has been added and is directed to implanting both the organ construct and transfected cells at multiple target sites.

The Office Action further asserts that:

> claim 27 recites the limitation "the cells," it is not clear which cells are being referenced, the initial population that is to be cultured on the matrix, or the second population that is to be transfected, or both.

Applicants thank the Examiner for pointing out this inconsistency and have amended claim 27 to recite "the first and second population of cells" to further indicate that either the cells that are cultured on the matrix material, or the cells that are transfected, can be myoblast cells. The Office Action further asserts that:

> Claim 29 recites the limitation "the tissue layer" in the first line of the claim. There is insufficient antecedent basis for this limitation in the claim.

Applicants thank the Examiner for pointing out this inconsistency and have amended claim 29 to recite "a" tissue layer, thereby rendering the rejection moot.

Rejection of Claims 1, 5, 6, 8, 10, 11 and 13 under 35 U.S.C. 102(a)

Claims 1, 5, 6, 8, 10, 11 and 13 are rejected under 35 U.S.C. 102(a) as being anticipated by Schuch *et al.* (Blood, Dec 2002).

In particular, the Office Action states that:

> Schuch et al teach a method of organ augmentation comprising transfecting a population of normal murine mammary gland (NMuMG) endothelial cells with a plasmid encoding a VEGF165 gene, cells were encapsulated in a polymer matrix ... encapsulated cells were then co-administered with Ml cells ... an undifferentiated myelocyte precursor subcutaneously to SCID mice. Tumors exposed to the constant release of VEGF165 showed an accelerated growth compared to non-VEGF-exposed tumors; therefore the VEGF induced assimilation and differentiation of cells in the target region.

Applicants respectfully traverse the rejection. As amended, the claimed invention is directed to a method of *organ augmentation* by *transiently* transfecting a population of cells with a plasmid encoding an angiogenesis modulating agent. The method then involves implanting the *transiently* transfected cells into a target tissue region where the cells express the angiogenesis modulating agent and induce assimilation and differentiation of cells in the target region.

Organ augmentation relates to improving the function of an organ such as a kidney or heart. Organ augmentation is described in the specification at page 15, line 31 through page 16, line 7, as:

> as increasing, enhancing, improving, the function of an *organ that is operating at less than optimum capacity.*" The term is used to refer to a gain in function so that the organ is operating at a physiologically acceptable capacity for that subject. For example, the physiological acceptable capacity for an organ from a child, *e.g., a kidney or heart*, would be different from the physiological acceptable capacity of an adult, or an elderly patient. *The entire organ, or part of the organ can be augmented. Preferably the augmentation results in an organ with the same physiological response as a native organ.* In a preferred embodiment, an organ is augmented in capacity when it is functioning to at least at 10% of its natural capacity (Emphasis added).

In contrast, Schuch *et al.* describe the role of VEGF and angiogenesis in the progression of acute myeloid leukemia (AML) using murine and human leukemic cell lines. Two mouse models were used. In the chloroma model, leukemic cell lines form chloromas (solid tumors) when injected subcutanously into SCID mice. The effect of VEGF on solid tumors was investigated in the chloroma model by encapsulating murine epithelial cells transfected with VEGF. The results show that the continuous expression of VEGF dramatically enhances the growth of the *solid tumor chloromas* (Page 4626, column 2).

In a separate leukemia model, the leukemic cell lines were injected intravenously into SCID mice to produce leukemia. In this model, VEGF was delivering by a viral vector. The effect of VEGF was to cause a "massive infiltration" of leukemic cells to the liver and spleen. There was also enhanced neovascularization in the bone marrow, associated with bone marrow infiltation of leukemic cells (Page 4627, column 1). From this, the authors conclude that AML progression is induced by VEGF.

Thus, the sole teaching in Schuch *et al.* is to grow tumors in a subject and the role of VEGF in tumor growth and cancer progression. The teachings in Schuch *et al.* simply contribute to the knowledge on how to inhibit tumor growth using VEGF antagonists. There is absolutely no teaching or suggestion for organ augmentation. Furthermore, the growth of solid tumors is

not the same as organ augmentation because a tumor is not an organ, and one would want to *inhibit* the growth of a tumor rather than *augment* it.

Accordingly, Schuch *et al.* fails to anticipate the claimed invention.

Rejection of Claims 1, 8 and 13 are rejected under 35 U.S.C. 102(b)

Claims 1, 8 and 13 are rejected under 35 U.S.C. 102(b) for being anticipated by Parmacek *et al.* (US Patent 6,297,221).

In particular, the Office Action states that:

> Parmacek et al teach a method of organ augmentation comprising transfecting a population of vascular smooth muscle cells with a plasmid encoding VEGF, an angiogenesis modulating agent, ex-vivo; and then implanting the transfected VSMCs into a subject (See col. 7, In 52-67) (Claims 1 & 13).
>
> Parmacek et al further teach that the transfected VSMCs onto a bioprosthetic graft or stent (which applicant calls a pharmaceutically acceptable carrier) (See col. 8, In 1-6) (Claim 8). Therefore the reference anticipates the claimed subject matter.

Applicants respectfully traverse the rejection. The claimed invention is directed to *organ augmentation* by *transiently* transfecting cells to express a VEGF angiogenesis enhancing factor. The expressed factor induces assimilation and differentiation of cells at the target site.

In contrast, Parmacek *et al.* simply describes isolating and characterizing a promoter, the SM22α promoter, specific for expression in smooth muscle cells. The SM22α promoter promotes transcription in both resting and proliferating cells, while other smooth muscle cell promoters are down-regulated in proliferating cells (*See* column 2, lines 49-59). Parmacek *et al.* describes the sequence of the promoter, and teaches how to link this promoter to an angiogenesis factor gene. Parmacek *et al.* further describes transfecting smooth muscle cells with the promoter and gene, and states that the expression of the angiogenesis factor promotes angiogenesis (*See* column 7, lines 52-59).

There is no teaching or suggestion in Parmacek *et al.* for organ augmentation. A mere teaching of using the SM22α promoter to express an angiogenesis factor in smooth muscle cells

is not the same as augmenting organ function. Furthermore, there is no teaching or suggestion for using a VEGF angiogenesis modulating agent. Accordingly, Parmacek *et al.* does not anticipate the claimed invention.

Rejection of Claims 1, 3-10, 23, 24-25 and 29 are rejected under 35 U.S.C. 103

Claims 1, 3-10, 23, 24-25 & 29 are rejected under 35 U.S.C. 103(a) as being unpatentable over Atala *et al.* (US Patent 6,479,064), in view of Yla *et al.* (Lancet, 2000), further in view of Cima *et al.* (J. Biomed Engineering, 1991) and Griffith-Cima (US Patent 5,709,854).

In particular, the Office Action states that:

> Atala et al teach a method of augmenting organ function comprising culturing a population of endothelial cells on a three-dimensional matrix to form an organ construct capable of differentiation in vivo to *replace* or augment organ function; and seeding a second population of parenchymal cells onto the matrix; and co-administering the cell populations by implanting the organ construct in vivo at a target site to induce assimilation and differentiation of cells in the target ... Though Atala et al teach using a retroviral vector to transfect either the parenchymal cells or endothelial cells with vector DNA encoding for the IL-1 or IL-2 angiogenesis modulating agents, it would have been obvious to one of ordinary skill in the art to alternatively use a plasmid containing the IL-1 or IL-2 genes ... One would have expected success performing the transfection using a plasmid because it is a well known and accepted method of transfection practiced in the art and Atala et al teach any accepted form of transfection is acceptable in their method (See, e.g., Yla et al, Pg. 213-214; See Atala et al col. 10, In 16-22). (Emphasis added).

Further that:

> it also would have been obvious to one of ordinary skill in the art at the time the invention was made to alternatively use three-dimensional matrices made from polymers such as polylactic acids or polyglycolic acids or combinations thereof (PLAs, PGAs, or PLGAs), such as those described by Cima et al.

Also that:

> Griffith-Cima at al provide another alternative to decellularized tissue in US Patent 5,709,854, where they disclose a matrix comprised of hydrogel, in which cells can be cultured and then subsequently injected into a patient to form an organ equivalent or tissue construct (See col. 1, In 27-58).

Applicants respectfully traverse the rejection. The claimed invention is directed to organ augmentation by transiently transfecting cells to express a VEGF angiogenesis modulating agent The expressed factor induces assimilation and differentiation of cells at the target site. As stated above, the invention relates to increasing, enhancing, improving, the function of an *organ that is operating at less than optimum capacity*. This gain in function results in an organ that is operating at a physiologically acceptable capacity for that subject. This is accomplished by injecting encapsulated cells transiently transfected with VEGF into target site such that the VEGF induces assimilation and differentiation of the cells at the target region.

Atala *et al.* describes how to prepare artificial organ constructs from decellularized scaffold matrices seeded with endothelial cells. These endothelial cells produce a vascular system that supports the growth of other cell populations. Atala *et al.* teach that these constructs can be made by using a decellularized biostructure of an "organ, or part of an organ" (Column 5, lines 34-35). Atala *et al.* also teaches decellularizing of an entire kidney and then using the kidney scaffold as a matrix for cell population. The entire cell seeded scaffold is then transplanted into a host (Example 6, column 19). Thus, the entire teaching of Atala *et al.* is for using tissue engineered implants that *replace* organs. To the extent that Atala *et al.* speaks of augmenting the tissue function, it is only in the context of replacing the organ or part of the organ with a cell seeded matrix.

Furthermore, there is no teaching or suggestion for organ augmentation by implanting transiently transfected cells that express a VEGF angiogenesis modulating agent. Thus, Atala *et al.* fail to teach or suggest the claimed invention.

This deficiency is not remedied by Yla *et al,* who simply describes using vectors for gene therapy. There is no teaching or suggestion for using angiogenesis modulating agents.

Cima *et al.* only provides a general discussion for restorable matrices made from polymers such as polylactic acids or polyglycolic acids or combinations thereof (PLAs, PGAs, or

PLGAs). There is no teaching or suggestion in Cima *et al.* for expressing a VEGF angiogenesis modulating agent to augmenting organ function.

Griffith-Cima only provides a general discussion for suspending cells in hydrogels. There is no teaching or suggestion for expressing a VEGF angiogenesis modulating agent.

For all the forgoing reasons, the references alone, or in combination fail to arrive at the claimed invention.

Rejection of Claims 1, 3-9, 23, 24 and 27-29 are rejected under 35 U.S.C. 103

Claims 1, 3-9, 23, 24 and 27-29 are rejected under 35 U.S.C. 103(a) as being unpatentable over Atala *et al.* (US Patent 6,479,064), in view of Yla *et al.* (Lancet, 2000), further in view of Lee *et al.* (Circulation, 2000). Specifically, that:

> Atala et al teach a method of augmenting organ function comprising culturing a population of endothelial cells on a three-dimensional matrix to form an organ construct capable of differentiation in vivo to *replace* or augment organ function; and seeding a second population of parenchymal cells onto the matrix; and co-administering the cell populations by implanting the organ construct in vivo at a target site to induce assimilation and differentiation of cells in the target ... Though Atala et al teach using a retroviral vector to transfect either the parenchymal cells or endothelial cells with vector DNA encoding for the IL-1 or IL-2 angiogenesis modulating agents, it would have been obvious to one of ordinary skill in the art to alternatively use a plasmid containing the IL-1 or IL-2 genes ... One would have expected success performing the transfection using a plasmid because it is a well known and accepted method of transfection practiced in the art and Atala et al teach any accepted form of transfection is acceptable in their method (See, e.g., Yla et al, Pg. 213-214; See Atala et al col. 10, In 16-22). (Emphasis added).

And that:

> Though Atala et al teach using a retroviral vector to transfect either the parenchymal cells or endothelial cells with vector DNA encoding for the IL-1 or IL-2 angiogenesis modulating agents, it would have been obvious to one of ordinary skill in the art to alternatively use a plasmid containing the IL-1 or IL-2 genes ... One would have expected success performing the transfection using a plasmid because it is a well known and accepted method of transfection practiced in the art and Atala et al teach any accepted form of transfection is acceptable in their method (See, e.g., Yla et al, Pg. 213-214; See Atala et al col. 10, In 16-22). (Emphasis added).

Also that:

> Lee et al teach a method of transfecting primary murine myoblasts with a VEGF gene, and then implanting the transfected cells, into the ventricular wall of SCID mice in order to induce angiogenesis at the site of implantation (See pg. 899, col. 1). It would have been obvious to one of ordinary skill in the art at the time the invention was made to form a construct, such as done by Atala et al, using the transfected myoblasts of Lee et al (Claims 27 and 38).

Applicants respectfully traverse the rejection. The arguments presented for Atala *et al.* are reiterated here in their entirety. There is no teaching or suggestion in Atala *et al.* for *organ augmentation* by implanting transiently transfected cells that express a VEGF angiogenesis modulating agent.

This deficiency is not remedied by Lee *et al.* who simply investigate the effect of continuous *constitutive* expression of VEGF in the myocardium using myoblast mediated delivery. The myoblasts are transfected with the VEGF and then implanted into the ventricular wall of mice. The abstract and the summary of this reference clearly teaches that *continuous* expression of VEGF results in the *formation of vascular tumors* at the implantation site. Lee *et al.* only highlight the problems associated with continuous expression of VEGF, they do not teach or suggest organ augmentation using a population of cells transiently transfected with a VEGF gene. Although, Lee *et al.* suggest the need for regulated expression of the gene, by using a *regulatable vector* system, this suggests that the vector promoter region can be switched on or off to control the expression of the gene. This does not suggest *transiently* transfecting cells with a gene that expresses VEGF for a time period, and then stops.

This deficiency is not remedied by Yla *et al,* who simply describes using vectors for gene therapy and does not even teach or suggest using angiogenesis modulating agents.

Rejection of Claims 1, 3 and 8-13 are rejected under 35 U.S.C. 103

Claims 1, 3 and 8-13 are rejected under 35 U.S.C. 103(a) as being unpatentable over Springer *et al.* (Gene Med, 2000), in view of Yla *et al.* (Lancet, 2000), further in view of Lanza *et al.* (US Patent 5,891,477). Specifically that:

> Springer et al teach transfecting a population of primary myoblasts with a retrovirus containing a VEGF gene, implanting the primary myoblasts stably expressing VEGF within alginate microcapsules coated with poly-L-lysine (which applicant calls a pharmaceutically acceptable carrier comprising a polymer matrix), and implanting the microcapsules under the skin and in the peritoneal cavity of SCID C.B-17 mice (See Springer et al, Pg. 280) (Claims 1, 8 and 10-13)...
>
> Though Springer et al uses a retrovirus to transfect the myoblast cells with the VEGF cDNA, it would have been obvious to one of ordinary skill in the art to alternatively use a plasmid containing the VEGF cDNA, as they are both art accepted means of transfecting cells (Claim 1)...
>
> While Springer et al teaches use of a simple microcapsule comprised of alginate and poly-L-lysine, Lanza et al provides a more comprehensive list of suitable microcapsules that may be used as pharmaceutically acceptable carriers.

Applicants respectfully traverse the rejection. Claim 11 has been cancelled, thereby rendering the rejection moot with regard to this claim.

Springer *et al.* teach that *constitutive* expression or long-term stable production of VEGF from encapsulated myoblasts, *retrovirally* transduced to express VEGF, results in hemangioma formation that have deleterious effects. (See Summary on page 549). In contrast to independent claim 1, and dependent claims thereto, which recites implanting *transiently* transfected cells with a plasmid encoding VEGF and *augmenting* organ *function*, Springer *et al.* does not teach the use of a plasmid containing VEGF cDNA, nor that organ *function* is *augmented.* Organ augmentation is defined throughout the specification (see, for example, page 15, line 31 through page 16, line 7) as increasing, enhancing, improving, the *function* of an organ that is operating at less than optimum capacity. Springer *et al.* merely shows that *constituitive* expression of *retrovirally* transduced cells can have deleterious results. See, for example, Springer *et al.* p 551, in which it is shown that "the legs injected with VEGF myoblasts (Figure 4A and 4B) now consisted primarily of hemangioma and pools of blood, with very few surviving β-gal-labeled

myofibers." Thus, Springer *et al.* does not teach organ function *augmentation* as required by the claimed invention, but rather that VEGF expression can have harmful effects.

Furthermore, Springer *et al.* teach the advantages of *retrovirally* transduced myoblast implantation, such as allowing for localized delivery, and the use of r*etroviral* transduction under the control of a regulatable promoter to allow for *precise control* of the time and delivery of expression to avoid the deleterious results reported in the Springer reference. Accordingly, one skilled in the art would not be motivated to use a plasmid system rather than the retrovirus system as discussed in Springer *et al.*

These deficiencies are not remedied by Yla *et al,* who simply describes using vectors for gene therapy. There is no teaching or suggestion whatsoever for using angiogenesis modulating agents, nor that transient transfection of VEGF can be used for organ aumentation.

Furthermore, Lanza *et al.* does not remedy the deficiencies of Springer *et al.* Lanza *et al.* provide a teaching of inhibiting fibrotonic rejection of implanted devices by administering non-steroidal anti-inflammatory agents. The reference also describes the formation of microcapsules, and the section referred to in the Office Action, only provides a general teaching of the pore size of gel matrices.

Since none of the cited references, either alone or in combination, teach all of the salient features of claims 1, 3 and 8-10, 12-13, as amended, the Examiner is respectfully requested to withdraw this rejection.

Rejection of Claims 1, 3 and 11-13 are rejected under 35 U.S.C. 103

Claims 1, 3 and 11-13 are rejected under 35 U.S.C. 103(a) as being unpatentable over Lee *et al.* (Circulation, 2000), in view of Yla *et al.*, (Lancet, 2000). Specifically that:

> Lee et al teach implanting primary murine myoblasts, transfected by a retrovirus with a murine VEGF gene, into the ventricular wall of SCID mice (See pg. 899, col. 1) (Claims 1, 12 and 13)...
>
> Though Lee et al does not specifically state stably transfected cells were chosen for implantation, it appears as if all cells transplanted were initially determined to be stably transfected. It would have been obvious to one of ordinary skill in the art at the time the invention was made to select only stably transfected cells for transplantation...

> Though Lee et al uses a retrovirus to transfect the myoblast cells with the VEGF cDNA, it would have been obvious to one of ordinary skill in the art to alternatively use a plasmid containing the VEGF cDNA, as they are both art accepted means of transfectiog cells (Claim 1).

Applicants respectfully traverse the rejection. Claim 11 has been cancelled, thereby rendering the rejection moot with regard to this claim.

Independent claim 1, and claims dependent thereto, are directed to *transiently* transfecting cells with a plasmid encoding a VEGF angiogenesis modulating agent. As discussed above, Lee *et al.* simply investigate the effect of continuous *constitutive* expression of VEGF in the myocardium using myoblast mediated delivery. The myoblasts are transfected with the VEGF and then implanted into the ventricular wall of mice. The abstract and the summary of this reference clearly teaches that *continuous* expression of VEGF results in the *formation of vascular tumors* at the implantation site. Lee *et al.* only highlight the problems associated with continuous expression of VEGF, they do not teach or suggest organ augmentation using a population of cells *transiently* transfected with a VEGF gene. Although, Lee *et al.* suggest the need for regulated expression of the gene, by using a *regulatable vector* system, this suggests that the vector promoter region can be switched on or off to control the expression of the gene. This does not suggest *transiently* transfecting cells with a gene that continuously expresses VEGF for a time period, and then stops.

This deficiency is not remedied by Yla *et al,* who simply describes using vectors for gene therapy and does not even teach or suggest using angiogenesis modulating agents.

Since the cited references, taken alone or in combination, do not teach each and every element of claims 1, 3 and 12-13, the Examiner is respectfully requested to withdraw this rejection.

Rejection of Claims 1, 3 and 11-13 are rejected under 35 U.S.C. 103

Claims 1, 3 and 11-13 are rejected under 35 U.S.C. 103(a) as being unpatentable over Springer *et al.* (Gene Med, 2000), in view of Yla *et al.* (Lancet, 2000). Applicants respectfully

traverse the rejection. Claim 11 has been cancelled, thereby rendering the rejection moot with regard to this claim.

As discussed above, Springer *et al.* teach that *constitutive* expression or long-term stable production of VEGF from encapsulated myoblasts, *retrovirally* transduced to express VEGF, results in hemangioma formation that have deleterious effects. (See Summary on page 549). In contrast to independent claim 1, and dependent claims 3, 12, and 13, which recite implanting *transiently* transfected cells with a plasmid encoding VEGF and *augmenting* organ *function*, Springer *et al.* does not teach the use of a plasmid containing VEGF cDNA, nor that an organ *function* can be *augmented*. Springer *et al.* focus on the deleterious effects of VEGF transduction and the need to have precise control over expression through a regulatable *retroviral* promoter.

These deficiencies are not remedied by Yla *et al,* who simply describes using vectors for gene therapy. There is no teaching or suggestion whatsoever for using angiogenesis modulating agents, nor that transient transfection of VEGF can be used for organ aumentation.

Since none of the cited references, either alone or in combination, teach all of the salient features of claims 1, 3 and 12-13, as amended, the Examiner is respectfully requested to withdraw this rejection.

Rejection of Claims 1, 2 and 13 are rejected under 35 U.S.C. 103

Claims 1, 2 and 13 are rejected under 35 U.S.C. 103(a) as being anticipated by Lazarous *et al.* (Cardiovascular Research, 1999), in view of Yla *et al.*, (Lancet, 2000).

> Lazarous et al teach a method of organ augmentation comprising the steps of: transfecting cells of canine pericardium using an adenovirus that encoded for human VEGF165, a known angiogenesis modulating agent; the transfection was performed *in vivo* by transcutaneous injection by way of a pericardial catheter (See Pg. 296, col. 1) (Claims 1 & 13). The measurable increase in VEGF expression lasted for only 14 days (See Pg. 297, col. 2 & Fig. 3) (Claim 2)... Current technique in molecular biology recognize the use of both viral vector and plasmid vector transfection as generally equivalent methods (See, e.g. Yla et al, Pg. 213-214); additionally, applicant provides in their specification acknowledgement of the use of an adenoviral vector as a preferred

embodiment for transiently transfecting cells for the claimed method (See Specification, Pg 73).

Applicants respectfully traverse the rejection. Claim 11 has been cancelled, thereby rendering the rejection moot with regard to this claim.

Lazarous *et al.* teach a gene transfer using adenovirus vectors for delivering VEGF to the cardiac cells to avoid the problems of systemic side effects VEGF. There is no teaching or suggestion in Lazarous *et al.* for organ function *augmentation*. Yla *et al.* only provides a teaching of plasmids and does not remedy this deficiency. Accordingly, the Examiner is kindly requested to withdraw this rejection.

Rejection of Claims 1, 3 and 13 are rejected under 35 U.S.C. 103

Claims 1, 3 and 13 are rejected under 35 U.S.C. 103(a) as being unpatentable over Isner *et al.* (WO 98/19712) in view of Yla *et al.*, (Lancet, 2000). Applicants respectfully traverse the rejection in light of the claim amendments.

As amended, the claimed invention is directed to *organ function augmentation* by *transiently* transfecting cells to express a VEGF angiogenesis enhancing factor. The expressed factor induces assimilation and differentiation of cells at the target site.

Isner *et al.* discloses methods for regulating angiogensis using endothelial progenitor cells. As stated by the Examiner "Isner et al. do not teach specific steps of transfecting the endothelial progenitor cells to express the endothelial cell mitogens." Furthermore, Isner *et al.* do not teach or suggest that *organ function augmentation* can be accomplished through *transiently* transfecting cells with a plasmid encoding VEGF, as recited by independent claim 1, and dependent claims 3 and 13. In fact, Isner *et al.* teaches away from using *transient* transfection on page 12, lines 22-24, where Isner *et al.* explicitly recites the use of *constituitive* expression of angiogenic cytokines.

These deficiencies are not remedied by Yla *et al,* who simply describes using vectors for gene therapy. There is no teaching or suggestion for using angiogenesis modulating agents.

In addition, there is simply no reason for a skilled artisan with knowledge of the Isner reference to look for systems of *transient* transfection. In order to satisfy the burden of obviousness in light of combination, the Examiner must show some objective teaching leading to the combination. The invention should not be employed as a blueprint to simply pick and choose elements from different sources to defeat patentability. While Isner *et al.* discloses methods of modulating angiogenesis comprising transplanting endothelial progenitor cells modified to express an endothelial cell mitogen, Isner *et al.* do not recognize problems associated with constitutive expression of VEGF. Thus, the skilled artisan would not be motivated to attempt *transient* transfection of VEGF

For all the reasons recited above, it is clear that neither the Isner *et al.* reference nor the Yla *et al.* reference discloses or suggests the methods of the present invention, that there is no motivation to combine these references, and that even if combined they do not disclose or suggest the method of the present invention. Thus, these references fail to disclose or suggest every element recited by independent claim 1. Because every limitation of an independent claim is imported to dependent claims, claims 3 and 13 are also allowable. Applicants, therefore, respectfully request that the Examiner withdraw all rejections.

Double Patenting

Claims 1, 5, 8, 10, 23-26 and 29 are provisionally rejected under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claims 11, 16, 17 and 18 of co-pending Application No. 10/292,166. The Examiner is respectfully requested to withdraw this rejection in light of the above amendments which render this rejection moot.

CONCLUSION

In summary, the above-identified patent application has been amended and reconsideration is respectfully requested for all the reasons set forth above. In the event that the amendments and remarks are not deemed to overcome the grounds for rejection, the Examiner is kindly requested to telephone the undersigned representative to discuss any remaining issues.

Respectfully submitted,

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Date: July 25, 2005

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